REMARKS

Claims 139-159 are pending. Claims 93-98 and 133-138 have been canceled. Claims 148-156 have been withdrawn from consideration. Claims 139-147 were rejected in the January 29, 2003 Office Action. New claims 157-159 have been added. Claim 146 has been amended. The new claims and claim amendment are fully support by the specification as originally filed.

The Examiner is thanked for the courtesy of the telephonic interview extended to Applicants undersigned representative on May 27, 2003. During that interview, the cited prior art reference (US Patent No. 6,403,312 to Dahiyat et al.) was discussed and compared to the pending claims. Applicants' undersigned representative discussed his belief that the computational source of diversity in the pending claims (cross-over between sequences of two or more parents) is fundamentally different from the source of diversity in the Dahiyat et al. patent (mutations in specific residues of a scaffold peptide) and, in fact, provides a patentable distinction. The Examiner stated that he felt that the Dahiyat et al. patent provided an implicit suggestion to computationally cross two parents by virtue of Dahiyat's discussion of *in vitro* synthesis of libraries containing the scaffold mutations. However, the Examiner also indicated that he would be willing to review the Dahiyat et al. reference again in light of any comments provided by Applicants. This response contains such comments.

In the January 29, 2003 Office Action, elected claims 139-147 were rejected under 35 U.S.C. § 103 as being unpatentable over US Patent No. 6,403,312 to Dahiyat et al. It is respectfully submitted that the pending claims are distinguishable from the Dahiyat et al. patent in multiple ways, and particularly in the source of diversity introduced by computation. Reconsideration of the rejection is respectfully requested.

The claims at issue each specify a method of identifying a set of oligonucleotides for use in an *in vitro* recombination procedure. The method involves various computational operations performed on data that identifies sequences of two or more parental polypeptides or parental nucleic acids that encode the polypeptides. Of relevance to this discussion, the method operations include

> . . . (b) computationally selecting one or more cross-over sites on the sequences . . .; thereby defining one or more recombinant polypeptides or recombinant nucleic acids that result from cross-overs between the parental polypeptides or nucleic acids at the one or more cross-over sites.

The Dahiyat et al. patent describes a computational method of introducing diversity in a "scaffold" peptide sequence by identifying specific amino acid residues for variation. The starting point for the process is a single "scaffold" sequence. Column 5, line 16 to column 6, line 46. Mutations in this scaffold at the identified residues are selected for a "primary library." Column 6, line 47 to column 14, line 39. Then combinations of these mutations are provided in various sequences to generate a secondary library. Column 14, line 40 to column 16, line 28. Each of these steps, including generation of the secondary library is performed computationally. Dahiyat et al. describe no other computational techniques of relevance.

According to Dahiyat et al., the members of the secondary library may be synthesized by various techniques. Column 16, line 42 to column 18, line 17. Some of these involve multiple PCR reactions using oligonucleotides. One specific example is gene shuffling with error prone PCR. See column 17, lines 53-67. These processes employ overlapping oligonucleotides, which correspond to the full length gene (scaffold). Column 16, lines 64-65. The oligonucleotides encode the variant amino acids introduced to the scaffold in the primary or secondary library (which were identified by computation). In some cases, there is a single variant amino acid in each oligonucleotide. See e.g., column 17, lines 17-19.

In the end, all the olignucleotides trace their sequences to a single scaffold and the amino acid variations computationally generated to produce the primary library. These oligonucleotides did not originate from multiple parent sequences. This is a fundamental distinction from the claimed invention. In the claimed invention, oligonucleotide(s) identified for *in vitro* recombination are chosen from a recombinant sequence derived from two or more parents, which were crossed.

The computational source of diversity in the Dahiyat et al. patent is limited to specific residue mutations within a scaffold. These are essentially point mutations. While Dahiyat et al. do provide a framework for selecting scaffold residues to vary and for choosing specific variations based on biochemical principles of the stability and activity, they fail to suggest that one might wish to computationally crossover the sequences of two or more parental biological molecules. Fundamentally, Dahiyat et al. are unconcerned with computational techniques that introduce diversity by any technique other than selecting specific residues for variation and choosing specific instances of new variable residues.

By performing crossover computationally, the present invention introduces a source of diversity that can mimic the positive features of *in vitro* recombination, without requiring as many rounds of synthesis and assaying. The benefits of

recombination include greater potential for preserving activity and desirable properties known to reside in parental sequences. Note that claim 146 specifies that the parental sequences "comprise naturally occurring polypeptides or naturally occurring nucleic acids." While the broadest claims do not make this requirement and can have known beneficial properties regardless, the invention of claim 146 specifies two or more naturally occurring parents and therefore employs portions of sequences known to survive in nature. This distinction further separates claim 146 from the Dahiyat et al. patent.

The Examiner acknowledges that the Dahiyat et al. patent does not disclose a computational recombination process. However, during the telephonic interview mentioned above, the Examiner stated his view that the *in vitro* nucleic acid synthesis (e.g., multiple PCR reactions) described in the Dahiyat et al. patent implicitly suggested the computational recombination recited in the pending claims. Applicants respectfully dispute this contention.

It is important to recognize that Dahiyat et al. describe a two-stage process, one that first employs computational techniques to identify primary and secondary libraries, and then employs *in vitro* techniques to produce nucleic acids encoding members of the secondary library. To the extent that Dahiyat et al. disclose crossover and recombination, it is limited to the *in vitro* side of the process.

Example 1 in the Dahiyat et al. patent explains their process in more concretely. As shown there, the computational stage of the process identified five different positions on a single scaffold protein for amino acid variation. The specific amino acids chosen for each of these positions are set forth in Table 4. In the *in vitro* stage of the process, 210 sequences corresponding to combinations of the five point mutations in the scaffold protein (TEM-1 gene for β-lactamase) were generated from overlapping oligonucleotides encoding the amino acid variations at the five sites.

In considering obviousness, a question that must be asked is why would one of skill in the art be motivated to perform a computational (first stage) crossover operation if it is equivalent to the *in vitro* (second stage) crossover already described by Dahiyat et al.? It is respectfully submitted that one of skill would not be led to replace Dahiyat's computational diversity generating step with a computational crossover step because to do so would render the computation step redundant. It is therefore respectfully submitted that Dahiyat's discussion of *in vitro* shuffling and recombination procedures does not suggest computationally selecting cross-over sites or defining recombinant polypeptides or nucleic acids as required by operation (b) of claim 139.

Features of a prior art reference must be applied in their proper context. One cannot take a first feature associated with one function of the prior art reference and replace it with a second feature from the same reference but associated with wholly different function. It would be improper to transpose Dahiyat's discussion of *in vitro* recombination (in the second stage) to the discussion of computational diversity generation (first stage) – unless there was some teaching to suggest this substitution. It is respectfully submitted that no such suggestion exists in the Dahiyat et al. patent.

In the Office Action itself, the Examiner makes the following argument as to why the Dahiyat et al. patent renders the elected claims obvious, even though it does describe "crossover":

> While Dahiyat et al. do not explicitly recite the term "crossover" as required by the instant claims, and do not explicitly indicate this procedure for generating recombinant sequences, the fact that particular sites are selected and allowed to change to other amino acid residues in order to generate mutant proteins would have made it obvious to an ordinary person in the art that those sites would have served as crossover sites, the wild type sequence and those with other amino acid residues at one particular position selected would have been parental sequences, and the resultant mutant sequences which would have different amino acid residues at all those positions selected would have been recombinants. Page 4 of the January 29, 2003 Office Action.

Applicants respectfully dispute this contention. First, it is not seen how the sites selected by Dahiyat et al. for changing amino acids "would have served as crossover sites." A crossover site generally represents the interface between segments of two different parent sequences. It is the point where the segments are joined. Choosing an amino acid position for variation within a scaffold template does not serve to define a crossover point for joining segments from two different parents.

Second, it appears from the Examiner's remaining remarks that he possibly views the scaffold as one parent ("wild type sequence") and the single amino acid variation for the site in question as originating with a second, undisclosed, parent. It is respectfully submitted that such reading is inconsistent with the well-understood meaning cross-over.

In the specification, cross-over is described as follows:

> CROSSOVER (RECOMBINATION)- This operator formally comprises joining a continuous part of one string with a continuous part of another string in such a way that one or two hybrid strings are formed (chimeras), where each of the chimeras contain at least two connected continuous string areas each comprising partial sequence of two different recombining strings. The area/point where sequence characters from different parental strings, is termed the crossover/recombination area/point. Page 17, lines 14-19.

As is consistent with the common meaning of crossover, this definition specifies that *continuous* portions of two separate sequences (strings) are joined. A single variant amino acid inserted into scaffold sequence would not be viewed by one of skill in the art as a continuous portion of a sequence.

It is also respectfully submitted that, contrary to the Examiner's assertion, the Dahiyat et al. patent does not suggest a second parent as the source of the replacement amino acid residue at the selected position. Dahiyat et al. describe a computational methodology for choosing such replacement amino acids. That methodology in no way relies on a "parent" sequence or obtaining a partial sequence of a parent sequence. In Dahiyat et al., there is no parent for the replacement amino acids.

In view of the above, it is respectfully submitted that the Dahiyat et al. patent does not render the claims unpatentable. Withdrawal of the rejection is respectfully requested.

While, it is believed that all claims submitted with the amendment of July 1, 2002 are patentable over the Dahiyat et al. patent, new claims 157-159 have been added to emphasize other features of the invention that are not suggested the Dahiyat et al. patent.

For the above reasons, it is respectfully submitted that pending claims 139-147 and 157-159 are allowable over the prior art. Applicants respectfully request a Notice of Allowance for this application.

As a final matter, it is noted that the Examiner has refused to examine the claims of groups II and III together. According to the Examiner, "the methods of identifying nucleic acids and a computer system have certainly acquired a separate status in the art as a separate subject for inventive effect and are usually published separately." Applicants understand and respect this position, but respectfully disagree. It is certainly inconsistent with the great majority of similar cases encountered by the undersigned representative in prosecuting both bioinformatics

method claims and corresponding "Beauregard" claims. (Note that Beauregard or "computer program product" claims are not normally viewed as computer systems, but rather as memory or other media on which instructions for carrying out a method are stored.) In numerous cases, the undersigned has not previously encountered an examiner who has issued and maintained a restriction between method and corresponding Beauregard claim groups. Applicants recognize that examination decisions by one PTO examiner are not used as precedent for other examinations. Nevertheless, Applicants felt that the Examiner might be interested in this information.

Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
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